REMARKS

Status of the Claims

Claims 18, 22-27, 30, and 36 are pending. Claims 31-35 and 37-38 are herein cancelled. No new matter has been added.

Claim Rejections – 35 U.S.C. § 103

The only rejection of the claims is that of claims 18-27 and 30-35 under 35 U.S.C. § 103(a) over *Willoughby et al.* (WO 94/23725) in view of *Pressato et al.* (WO 97/07833). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

1. *Willoughby et al. does not disclose that hyaluronic acid alone is therapeutically effective to inhibit angiogenesis.*

The Examiner states that "*Willoughby et al.* disclose that the hyaluronic acid is therapeutically effective or component for inhibiting or treating angiogenesis (see abstract)." (Office Action, page 4). The Examiner has completely disregarded the plain meaning of the language in the abstract. The Abstract states:

> The use of: (a) a non-steroidal anti-inflammatory agent, **and** (b) . . . esters . . . of hyaluronic acid in a therapy wherein dosage amounts taken from the composition each comprise (1) a therapeutically effective amount of component (a); **and** (2) a therapeutically effective amount of . . . esters . . . of hyaluronic acid.

(*Willoughby et al.*, Abstract, emphasis added). The use of the word "and" clearly indicates that the NSAID is intended to be administered with the hyaluronic acid. The Examiner cites to claims 41 and 48, however, *Willoughby et al.* itself states that "the administration of hyaluron (HA) alone . . . exhibited no significant effect on the tissue vascularity." (*Willoughby et al.*, page 17, lines 32-34). Thus, one of skill in the art would believe from the reference itself that hyaluronic acid did not inhibit angiogenesis.

As discussed in the response of October 1, 2008 (pages 7 and 8), this is supported by the subsequent publications *Willhauck et al.* and *Alam et al.* (which discusses the same data as disclosed in *Willoughby et al.*). The Examiner has not indicated that he considered the teachings of these two papers at all. Instead, the Examiner blithely ignores evidence within *Willoughby et al.* itself and in the art which teaches away from the claimed invention.

This adherence to a construction of the references which is factually inaccurate is improper and not only suggests that the Examiner is improperly relying on hindsight, but that the Examiner is impermissibly substituting his judgment for those of skill in the art and is not analyzing the references as a whole. Applicants therefore request that the Examiner withdraw the rejection.

2. *The formation of granulation tissue does not necessarily result from the administration of an ester of hyaluronic acid.*

The Examiner concedes that *Willoughby et al.* does not teach a specific ester of hyaluronic acid. (Office Action, page 4). However, the Examiner states that the formation of granulation tissue resulting from the inhibition or regression of angiogenesis would be inherent with the administration of an ester of hyaluronic acid. (Office Action, page 5). Applicants respectfully disagree.

Applicants herein enclose three scientific papers published after the filing of the present pending application which indicate that partial Hyaff 11 (a partial benzyl ester of hyaluronic acid) **stimulates** angiogenesis rather than inhibiting angiogenesis as claimed. (See attached, *Barbucci et al.* (Published September 2, 2002), Abstract and page 3091 col. 1, lines 23-24; *Colletta et al.* (2003), Abstract and page 359, col. 2, lines 24-27); and *Taddeucci et al.* (2004), Abstract and page 204, page 1, col. 2, line 26). Further, *Taddeucci et al.* teach that a partial benzyl ester of hyaluronic acid stimulates angiogenesis.

Willoughby et al. generically discloses that "hyaluronic acid and/or salts thereof and/or homologues, analogues, complexes, esters, fragments, and subunits of hyaluronic acid" (*Willoughby et al.*, Abstract) might be useful in a composition with a NSAID to inhibit angiogenesis. However, *Willoughby et al.* is incorrect. The Specification and evidence establish that while the total benzyl ester of hyaluronic acid inhibits angiogenesis, at least some forms of hyaluronic acid (including partial benzyl esters of HA) actually stimulate angiogenesis.

Further, *Pressato et al.* does not suggest the use of a total benzyl ester for inhibiting angiogenesis. *Pressato et al.* discloses two types of Hyaff (benzyl ester), that is, Hyaff partially and totally esterified also with two types of alcohol to produce a mixed ester (*Pressato et al.*, page 9, lines 8-25 of the PCT specification, examples 3 and 4). *Pressato et al.* also discloses the use of HA derivatives in combination with other, also non-biodegradable derivatives at page 6, beginning at line 28.

The broad generic disclosure of *Willoughby et al.* directed to the use of a large number of potential "salts", "homologues, analogues, complexes, esters, fragments, and subunits of hyaluronic acid" cannot be properly considered to suggest Applicants' unexpected finding that the total benzyl ester is useful in the claimed method, when even the partial benzyl ester is not.

However, the evidence shows that a partial benzyl ester of hyaluronic acid can stimulate angiogensis, a result which is directly opposite to the purpose and treatment as presently claimed. Accordingly, one of skill would have no reasonable expectation of success in achieving the claimed invention based on the combination of *Willoughby et al.* and *Pressato et al.*.

The Examiner has provided no plausible reason why one of skill would 1) chose an ester for the treatment of cancer (as opposed to some other form of HA or surgical adhesion), 2) think that a benzyl ester would have any effect on angiogenesis, or 3) think that the administration of hyauronic acid (its ester or any other form) alone would have an effect on angiogenesis.

Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

In view of the above, Applicant submits that the Examiner's *prime facie* case of obviousness is improper and should be withdrawn.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: November 6, 2009

Respectfully submitted,

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Attachments: Barbucci et al. (Published September 2, 2002);
Colletta et al. (2003);
Taddeucci et al. (2004)